Diagnostic value of BAL in PAP

Several studies have shown the major value of BAL in the diagnosis of PAP [196–198].

On gross examination, the BAL fluid has a milky appearance. After gravity sedimentation a dense tan sediment can also be observed. On light microscopy, the analysis of recovered cells shows an increase in total cell count [199–1009] probably partially explained by the fact that, in these studies, the majority of patients were smokers. On cytocentrifuged slides stained by MGG, the striking feature is the finding of a variable amount of basophilic extracellular deposit mixed with enlarged foamy alveolar macrophages (AM), crystal clefts and cellular debris. This extracellular material as well as the cytoplasmic content of the AM show a pink PAS positive diastase resistant staining. It should be noted that this staining is weaker than that observed in transbronchial biopsy (TBB) or open lung biopsy due to the dilution induced by the BAL fluid.

On electron microscopy the ultrastructural appearance is characteristic, with small lamellar bodies of wavy or regular periodicity, tubular myelin structures and myelin-like multilamellated structures with electron dense central region [101–102]. Added to this extracellular material, ghost cells, AM and/or pneumocytes II are filled with intracellular bodies and empty vacuoles or grey lipid droplets.

Different cellular profiles have been described. Some authors found an increase of lymphocytes compared to a control group with similar smoking habits [200] with an increased ratio of helper to suppressor T-cells. Others found a slight increase in neutrophils [203]. Particularly in these latter cases, a careful search for pathogens has to be undertaken.

In order to differentiate primary from secondary PAP, some authors have proposed an analysis of the alveolar material with specific antibodies against surfactant apoproteins. They have shown a significant difference in the quantity and repartition of the staining between primary and secondary forms [204].

Biochemical analysis of the lavage fluid, in particular protein and lipid analysis, have been performed by many laboratories. In comparison with normal subjects, a higher protein and phospholipid concentration is always present, and qualitative abnormalities in phospholipid composition have been found [53, 205]. Some authors have shown an impairment in AM function [199, 206].

The value of BAL in comparison to other diagnostic procedures in PAP

Few papers have compared the advantages of the different diagnostic procedures in PAP. However, in comparison with sputum analysis, transbronchial biopsy (TBB) or open lung biopsy, they have emphasized the major value of BAL [196, 197, 201, 202]. This is mainly due to the fact that PAP is an intra-alveolar disease and that, for instance, segmental BAL covers a larger distal lung field than TBB, the latter being sometimes equivocal if the disease is patchy. Nevertheless, the combination of both procedures will assure proper diagnosis. However, as TBB can induce alveolar space oedema and focal haemorrhages, BAL should be performed first.

The value of BAL in the follow-up and treatment of PAP is reported in the chapter dealing with therapeutic applications

Conclusions

Compared with other pulmonary disorders, PAP is certainly that in which BAL has a very high diagnostic yield, making open lung biopsy in most cases unnecessary. Furthermore, BAL is also of major value in the follow-up and the therapeutic management of patients with PAP.

The clinical role of BAL in pulmonary haemorrhages

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Many different clinical syndromes are included under the general heading of pulmonary haemorrhages (PH) and haemosiderosis (table 1). The triad of haemoptysis, infiltrates on chest X-ray and anaemia are present in most of the cases, however active PH does occur without these findings.

Furthermore, a delay in diagnosing PH can lead to fatal renal or pulmonary complications. Therefore, a rapid diagnosis is important and BAL appears to be the method of choice especially to diagnose distal occult PH and to eliminate other underlying diseases such as infections or malignancies.

Diagnostic value of BAL in pulmonary haemorrhages

On gross examination, the BAL fluid has either a bloody or orange-pink colour, or can be of normal translucent appearance.

On light microscopy, compared with nonsmoking controls, the total cellular count and the percentage of AM are increased [207]. Several morphological aspects can be observed such as free red blood cells, red blood cells in alveolar macrophages (AM) and haemosiderin laden AM. The importance of the haemosiderin content can be evaluated either by the percentage of AM

Table I – Principal disorders associated with diffuse pulmonary haemorrage (PH) and haemosiderosis

1. PH secondary to cardiac disease, intrapulmonary vascular lesions or malformations.
Chronic left- or right-sided heart failure (mitral stenosis).
Pulmonary hypertension.
Pulmonary veno-occlusive disease.
Pulmonary lymphangiomyomatosis.
Arteriovenous fistulas or other congenital vascular malformations.
Vascular thrombosis with infarction.

2. Pulmonary haemosiderosis and glomerulonephritis.
With anti-basement membrane antibody (ABMA) disease.
Without ABMA.
With immune complex-mediated.

3. Idiopathic pulmonary haemosiderosis.

4. PH associated with vasculitides and collagen vascular disease.
Systemic lupus erythematosus.
Wegener granulomatosis.
Mixed connective tissue disease.
Idiopathic thrombocytopenic purpura.

5. PH associated with miscellaneous disorders.
Diffuse necrotizing infections.
Severe coagulopathy.
Malignant diseases such as acute leukaemia.

6. PH associated with drugs.
D-penicillamine.
Amphotericin B
Chemotherapy drugs

containing haemosiderin or by a score proposed by GOLDE and co-workers [208, 209]. This haemosiderin score (HS) is based on the colour intensity of AM cytoplasm on an iron stain (*i.e.* Prussian blue).

The presence of intact red blood cells in the lavage fluid is not in itself a definite sign in favour of AH, it can be related simply to minor trauma during the bronchoscopy. However, in acute PH such as in Goodpasture's syndrome, BAL can be bloody without haemosiderin laden AM [210]. In fact, rather than a bloody BAL fluid, free red blood cells or red blood cells in AM, it is the presence of numerous haemosiderin laden macrophages, appearing at least 48 h after bleeding, which strongly suggests pulmonary haemorrhage [211]. When one observes not only a large increase in the percentage of AM containing haemosiderin deposits, but also an increase in the intensity of the haemosiderin content (HS >100), the diagnosis of alveolar haemorrhage can be confirmed. In the evaluation of the bleeding, this HS appears more sensitive [207, 212]. In fact, in many pulmonary disorders without significant bleeding, light haemosiderin deposits can be observed, even in a large percentage of AM (such as in immunosuppressed patients).

Comparison of BAL and other diagnostic procedures in PH

Few papers have compared the advantage of the different diagnostic procedures in AH. Compared with transbronchial biopsy (TBB) or open lung biopsy, they have mostly emphasized that BAL is a less invasive technique, particularly important in patients with low platelet counts or bleeding disorders, where biopsy may often be impossible because of the high risk of bleeding [207, 208].

Some authors [207, 212] have compared the haemosiderin score (HS) in BAL [208] and pulmonary parenchyma obtained by TBB, open lung biopsy and from post-mortem specimens. They have shown that in BAL HS was a very good marker of pulmonary haemorrhage. In particular, a high HS is always associated with histological evidence of severe pulmonary haemorrhage. KAHN *et al.* [207] conclude that an HS greater than 100 is indicative of severe pulmonary haemorrhage. On the contrary, there is no correlation between the bloody appearance of the BAL fluid or large number of red blood cells per mm^3 and either an elevated HS or the presence of alveolar haemorrhage in tissue specimens.

Conclusions

BAL appears to be the method of choice to confirm pulmonary bleeding especially in occult alveolar haemorrhages and to search for an underlying disease such as infection or malignancies. It is a safe procedure with minimal and rare complications particularly in patients with low platelet counts or bleeding disorders and can be performed in virtually all cases regardless of the severity of the disease.

Drug induced pneumonitis

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Since the list of drugs that may adversely affect the lung grows longer every day, the problem is not to be exhaustive in naming every one of them but to have reliable criteria by which to suspect and to recognize an iatrogenic lung disease early enough to prevent the development of irreversible injury [213, 214]. In this context, BAL has proved to be a very useful tool in the diagnostic approach. It can provide evidence to differentiate between iatrogenic causes, and to distinguish these from infectious or malignant aetiologies.